Structural Studies of the Vitamin D Receptor DNA Binding Domain

P. Shaffer, D. Gewirth (Duke U. Medical Center)

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Introduction: The vitamin D receptor (VDR) is a prototypical member of the steroid and nuclear hormone receptor superfamily. In response to the high affinity ligand 1,25 dihydroxyvitamin D3, it modulates the transcription of hormone responsive genes, many of which are involved in the regulation calcium homeostasis in the body. The vitamin D receptor is a modular transcription factor, with distinct domains for DNA binding and DNA-dependent dimerization, and ligand binding and DNA-independent dimerization. In the unliganded state, the receptor forms a homodimer on DNA and does not stimulate transcription. In the liganded state, the homodimer is unfavored and instead a heterodimer is formed with the retinoid X receptor (RXR). Both the homodimer and heterodimer bind to the same DNA targets, which consist of a direct repeat of a hexameric half sites separated by three base pairs of spacer sequence. We are interested in examining the stereochemical basis for the DNA-dependent dimerization of the VDR, and in particular the mechanism by which it recognizes DNA targets with three base pairs of spacer.

Methods and Materials: We have grown several crystal forms of the homodimeric VDR dbd-DNA complex. The best crystals belong to space group P4(3)2(1)2, with a = b = 61.7 Å, c = 243.7 Å and contain one complex per asymmetric unit.

Results: Diffraction data were collected to 2.7 Å at NSLS Beamline X25. The structure of the complex was solved by molecular replacement and is currently under refinement. Dramatically larger crystals of the complex have been grown recently and should yield high resolution diffraction.